219 Special Screening Tests

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Definition

The tests discussed in this chapter may be used to screen for disease in asymptomatic individuals. *Screening* involves testing an unselected population for the presence of a particular condition. When physicians test only patients who seek their services, this is not truly an unselected population and the term *case finding* would more properly apply.

Before a screening test is recommended widely, it must be measured against certain criteria:

- The disease that is sought must cause significant morbidity and mortality.
- Treatment must be available.
- The disease must have an asymptomatic period during which treatment would improve the outcome compared to that which would be achieved if the disease were not diagnosed until it caused symptoms.
- The benefits of making the diagnosis must clearly outweigh the risks.
- The cost of testing cannot be excessive.

It cannot be emphasized enough that the guidelines presented here are for the testing of asymptomatic individuals. They would not necessarily constitute an adequate evaluation of patients with symptoms and might also be inadequate for patients who are at a particularly high risk for one of these conditions. Rather than create yet another set of guidelines, those of the U.S. Preventive Services Task Force will be summarized for the studies under discussion. These guidelines are much less aggressive than those of some other groups, such as the American Cancer Society.

- *Proctosigmoidoscopy and stool occult blood test:* There is insufficient evidence to recommend for or against these studies for the general population. These studies, or in some cases colonoscopy, may be indicated for those with risk factors.
- *Mammography:* Test women every 1 to 2 years beginning at age 50 and concluding at about age 75, unless pathology has been detected. Begin earlier in women at high risk.
- *Pap smear:* Begin testing at onset of sexual activity and repeat every 1 to 3 years. Discontinue at age 65 if previous smears have been consistently normal.
- *Cholesterol:* Test all adults.

Proctosigmoidoscopy

Technique

Proctosigmoidoscopy is generally performed with a 35 cm flexible scope. Patients should have the indication for the procedure discussed with them as well as a brief description of the procedure and its risks. The primary risk to the otherwise healthy patient is perforation, but this occurs in probably less than one per 5000 examinations. The small risk of infection or bacteremia would be of concern primarily to the immunocompromised patient or to one with a significant cardiac valvular abnormality or prosthesis.

The preparation consists of one or two Fleet's enemas just before coming in for the procedure, usually after an overnight fast. Immediately before the examination, the instrument should be checked for visual clarity and proper function of its light source, suction, air insufflation, and tip deflection. The last few centimeters of the shaft of the scope, but not the tip, should then be lightly coated with lubricant.

The patient should be placed in the left lateral decubitus position. A digital rectal examination is performed. With the examining finger still in the anal canal, the tip of the scope is carefully inserted over the finger; the proximal end of the scope is supported and controlled with the left hand. The right hand is positioned toward the distal end of the shaft of the scope to advance it when appropriate. The scope is quickly inserted to maximal penetration, using air insufflation as needed. Of course, continued insertion should progress only as long as the lumen of the bowel is clearly visible. If it is not, the scope is withdrawn until the lumen comes into view. Most of the examination is performed during scope withdrawal. Complete 360-degree sweep of the wall of the bowel is carried out repeatedly during the withdrawal phase.

Basic Science and Clinical Significance

Colorectal cancer is a surgically curable disease when detected in its localized stage (Dukes A or B1). Long-term survival decreases significantly once the tumor has spread to the bowel serosa (Dukes B2), to the lymph nodes (Dukes C), or to distant sites (Dukes D). Rectal carcinomas have a slightly worse prognosis than those in the colon.

About 80% of cancers found in proctosigmoidoscopy screening programs have been in Dukes stage A or B, although the distinction between B1 and B2 has not been made. Nevertheless, this compares favorably with cancers detected outside of screening programs, which are Dukes C or D in 60% or more of cases. Familial colonic polyposis and Gardner's syndrome are inherited disorders in which

multiple colonic polyps develop and eventually transform into adenocarcinoma. Prophylactic colectomy is recommended in these conditions. Other risk factors for colonic carcinoma include a family history of colon carcinoma, the presence of the cancer family syndrome, or personal history of previous colon adenomas, carcinoma, or also breast and some gynecologic malignancies.

Another benefit derived from proctosigmoidoscopy screening programs is the diagnosis of benign neoplasms. One very large study removed all polyps found during serial examinations. Only 15% of the anticipated number of cancers of the lower bowel developed during the study period, lending support to the concept that removing benign neoplasms may prevent the development of cancer. In addition, patients having one polyp are known to be at higher risk of having additional polyps or cancer elsewhere in the bowel and are more likely to develop additional polyps later. Once these high-risk patients are identified, serial colonoscopic evaluation can have further benefit. It should be emphasized, however, that there are no randomized studies that prove a reduction in mortality with proctosigmoidoscopy.

The yield for finding invasive cancer with rigid proctosigmoidoscopic screening is low, occurring in about 0.1 to 0.2% of examinations. But benign neoplasms can be found in from 3 to 9% of examinations.

Decades ago, one-half of the colorectal carcinomas were thought to be located within the reach of the examining finger and two-thirds were within the theoretical reach of the rigid sigmoidoscope. More recent data have shown that fewer than 20% of colorectal cancers can be found by digital examination and fewer than 50% are located within 25 cm of the anus. Multiple studies with rigid sigmoidoscopes by experienced examiners have demonstrated the true average depth of penetration to be less than 20 cm. For these reasons, longer flexible sigmoidoscopes have become the preferred method for screening examination.

Both 60 cm and 35 cm flexible sigmoidoscopes are currently available. Compared to the rigid scope, the 60 cm flexible scope has achieved nearly three times the average depth of penetration with a corresponding tripling of the yield for both benign neoplasm and carcinoma. Most of these studies, however, have been done by experienced endoscopists. The 35 cm flexible scope has been shown to achieve depths of penetration of well over 25 cm by totally inexperienced examiners and over 30 cm by nonendoscopists who have experience with the flexible scope. Because the 35 cm scope will predictably visualize the most high-risk area of the bowel, its yield is not a great deal lower than that of the 60 cm scope.

Stool Occult Blood Testing

Technique

The first bowel movement on each of 3 consecutive days is tested. The testing period is extended if the patient does not have a bowel movement each day. The stool specimen should be caught or in some way prevented from making contact with the water in the toilet. Two sites from each bowel movement are tested.

Each specimen is smeared on guaiac-impregnated filter paper. This is covered and stored until all specimens have been collected. The patient must return these specimens promptly after the final collection. A developing solution of hydrogen peroxide and denatured alcohol is applied to the reverse side of the paper. Hemoglobin has peroxidase-like activity that will oxidize the guaiac to a blue compound.

Red meat can frequently cause Hemoccult tests to turn positive and must be strictly avoided in the days before and during the collection. Foods with high peroxidase activity, such as turnips and horseradish, are also best avoided, as are anti-inflammatory drugs that can induce some gastrointestinal bleeding. Iron can cause a positive test, and induced bleeding is probably the most important mechanism here too. Testing should obviously be avoided during menses or when there is an active hemorrhoidal problem. The antioxidant ascorbic acid can yield falsely negative results and should likewise be avoided. Delays in testing can also cause false negative results.

Rehydration consists of adding a drop of water to the guaiac paper before adding the developing solution. This increases sensitivity but decreases specificity. Testing loose stools or stools that have been immersed in toilet water has the same effect. Some commercially available kits instruct patients to test stools from the toilet bowl.

HemoQuant is a more reliable but also more costly method of improving the sensitivity of stool occult blood testing. With HemoQuant, all fecal hemoglobin is reduced to porphyrin, which is then measured fluorimetrically. The amount of hemoglobin in the stool can be calculated from the porphyrin value. The test is affected by red meat but not by peroxidase-containing foods. Very dry stools, because of concentration, will slightly increase the hemoglobin values estimated to be in the stool.

Basic Science and Clinical Significance

As emphasized in the discussion on proctosigmoidoscopy, a major barrier to the control of colorectal cancer is that, outside of screening programs, the cancer has spread beyond a local area in all but 40% or less of cases before diagnosis. As with the proctosigmoidoscopy studies, cancers detected by stool occult blood testing programs are still localized in about 80% of cases. Again, benign neoplasms will be detected much more often than carcinomas, and removal of these polyps and serial colonoscopic follow-up of these higher-risk patients should help prevent the development of cancer. As with proctosigmoidoscopy, it should be emphasized that there are no randomized studies that prove a reduction of mortality with stool occult blood testing.

About 4% of older individuals tested will have at least one slide positive for occult blood. Just under one-half of these people will have a neoplastic condition, mostly nonmalignant polyps. Only about 5 to 10% of people with positive slides (0.2 to 0.4% of people tested) will have an invasive carcinoma. The predictive value of stool occult blood testing for neoplasia (malignant and nonmalignant) increases with age. In the 40- to 49-year-old age group the predictive value is less than 30% but it rises to well above 50% in those over 70 years old.

Stool Hemoccult testing is negative in about one-third of patients with invasive cancers. Polyps bleed less frequently than cancers, and the smaller the polyp, the less likely it is to bleed. Nevertheless, because there are so many more people with small polyps than with large polyps or cancers, small benign polyps are the most common neoplastic cause of stool occult blood.

HemoQuant and the Hemoccult test with rehydration both require a very strict diet, especially total abstinence from red meat, which makes them unsuitable for large-scale screening. In certain individual cases where compliance is assured, however, they may be preferred over the standard Hemoccult test.

Mammography

Technique

At present, the most commonly used method of performing mammography is the screen-film technique. This study requires a dedicated mammography unit having a molybdenum anode x-ray tube with a finely calibrated focal spot for x-ray emission rather than a tungsten anode tube used with standard radiographs. This technique enhances the contrast between breast tissues and at the same time requires very low doses of radiation. Breast compression is required which may result in modest discomfort. In premenopausal women mammography is best scheduled during the week after menstruation, particularly in patients who have experienced severe premenstrual breast tenderness.

Basic Science and Clinical Significance

Long-term survival in breast cancer correlates with axillary lymph node status at the time of diagnosis. Ten-year survival is about 80% in patients with negative nodes, compared to about 40% for those whose nodes are positive.

The risk factors for breast cancer of particular relevance are a personal history of breast cancer, breast cancer in a first-degree relative, a history of benign proliferative breast disease, and having no pregnancy before age 30.

Screening with breast examination and mammography in women over age 50 has been shown to decrease deaths from breast cancer in the randomized controlled Health Insurance Plan (HIP) study begun in 1963. Use of death as an endpoint for the study has removed concerns about length bias (i.e., diagnosing very slow growing cancers that would never have resulted in deaths) and lead time bias (i.e., diagnosing a fatal cancer earlier without changing its outcome in any way).

The usefulness of mammography in women age 40–49 remains controversial. An 18 year follow-up in the HIP study suggests some late benefit in this 40–49-year-old group. The significance of this is unclear.

Data from a large multicenter screening program in the 1970s (with presumably better radiologic equipment and more experience in interpretation) showed mammography to be more sensitive than in the 1960s study. Many more tumors were found in the 40- to 49-year-old group and there were many more minimal cancers (noninfiltrating tumors or infiltrating tumors less than 1 cm) with negative axillary nodes in all age groups. This has led to speculation that there is even more to be gained by aggressive screening because of the more advanced state of the technology. Concerns have been raised, however, that the natural history of these minimal cancers is not known to be the same as for other breast cancers. These arguments have been countered by statistics showing that although the prevalence was high (because of slow-growing tumors and symptomatic patients volunteering for screening), the incidence was consistent with the number predicted.

Cancer of the breast is known to increase in frequency with age; as expected, the multicenter screening program found many more cancers in older patients. But the randomized study did not enter patients over the age of 64. Some recent studies have suggested benefit to mammographic screening beyond age 65. There is no good evidence of benefit to testing the very elderly who have had previously normal studies.

There is no proof that radiation in the dosages used for mammography increases the risk for breast cancer. Japanese women exposed to the atomic bomb, radium dial workers, tuberculosis patients in sanatoriums who had frequent fluoroscopies, and women treated with radiation for nonmalignant breast conditions have been studied. There are insufficient data on doses of under 100 rads. Certainly doses over 100 rads predispose to breast cancer. Women over ages 30 to 40 are markedly less sensitive to the radiation effect, and when malignancies are produced, they do not begin until 10 to 15 years after the radiation exposure. Even if the linear relationship between breast cancer and radiation exposure extends down to those receiving very low dosages, the frequency for women over age 40 would be 3.5 to 7.5 cancers per million women per year per rad after a 10 or more year delay. Since, for example, breast cancer attacks women age 65 at a rate of 2500 per million women per year, the patient-years lost to radiation-induced cancer would be immeasurable compared to the patient-years saved by screening.

The high cost of mammography remains the main obstacle to its widespread utilization. Though the test can be performed relatively inexpensively in a high-volume screening program, few of these programs are currently available. It should be remembered, however, that there is at least partial return on the dollars spent on mammography from the lower medical expenses generated by those women who benefit from screening.

Pap Smear

Technique

The pap smear is performed during the pelvic examination with the cervix visualized through the vaginal speculum. No lubricant should have been used on the examiner's gloves or the speculum. Ideally, the patient should not have douched for 48 hours and should not be menstruating, but these are certainly not contraindications. If the cervix is covered with mucus or discharge, this can be cleared by lightly dabbing with a large cotton swab.

Two specimens should be obtained. A cotton swab is inserted into the endocervical canal and lightly rotated as it is being withdrawn. The swab is then gently rolled on a glass slide. The second specimen is obtained by inserting one tip of an Ayre spatula into the cervical os and rotating it a full 360 degrees. The specimen is smeared onto a second slide or a different portion of the same slide. These must be promptly sprayed with a fixative.

About 90% of cancer of the cervix is of the squamous cell type, which arises from the transition zone between squamous and columnar epithelium. This transition zone, which may be well up into the cervical canal or readily visible on the surface of the cervix, is the area to be tested. An adequate pap smear should contain endocervical cells, confirming that the examiner has reached to and beyond the transition zone.

To interpret the smear properly, the laboratory must be provided with the patient's age and the date of her last menstrual period. They must also be told if the patient is pregnant, is on hormonal therapy, is wearing an intrauterine device, or has had previous malignancy, surgery, or radiation.

Basic Science and Clinical Significance

The unique feature of cervical cancer is the remarkably long (10 or more years) period during which carcinoma in situ can exist before becoming frankly invasive. Carcinoma in situ of the cervix is most frequent in women in their early to mid-30s, many years before the usual age for invasive cancer of the cervix. The identification of the in situ phase by pap smear testing has resulted in a dramatic decrease in the frequency of invasive carcinoma. In only about 5% of cases does rapid progression to invasive cervical cancer occur.

Carcinoma in situ of the cervix is a completely curable condition. On the other hand, carcinoma of the cervix has a 5-year survival of over 80% when locally invasive and 45% when regionally invasive.

Early age of first sexual intercourse and multiple sexual partners are factors that increase the risk of cervical cancer. The promiscuity of male partners may also be an important factor. Women who have never had sexual intercourse, or who are beyond 60 years of age with normal previous pap smears, or who have had a hysterectomy for a nonmalignant disease, are at very low risk for cervical malignancy.

Cytologic interpretation of pap smears is inexact, with variability in interpretation. Also, definite pathologic abnormalities present on one slide are not invariably present on another slide from the same patient. Obtaining specimens from both the endocervical canal and the exocervix, and repeat testing yearly at least initially, help obviate concerns about false negative results. False positives can occur because of variability in interpretation, and carcinoma in situ in some cases does appear to resolve spontaneously. This happens quickly, within months, if it does occur.

Controversy has arisen recently because some medical organizations, most notably the American Cancer Society, have changed their routine recommendations for pap smear testing from the traditional once a year to once every 3 years after 2 yearly normal smears. The criticism of this recommendations has focused primarily on the large number of women in the general population who are at high risk because of their sexual history.

Cholesterol Screening

Technique

The techniques involved in cholesterol testing are discussed in detail in Chapter 31.

Basic Science and Clinical Significance

It has long been known that hypercholesterolemia is associated with premature coronary artery disease and its sequelae, but until recently there has been no convincing evidence that patients derive any benefit from having their cholesterol levels decreased by diet or drug therapy. New data seem to provide this much needed proof. Three randomized studies have now demonstrated a reduction in cardiac events by lowering serum cholesterol. Each of these studies used drugs to achieve these reductions (Clofibrate, Cholestyramine, and Gemfibrozil). The Clofibrate study entered men aged 30–59 with cholesterol levels in the upper third of those screened. Triglycerides were not usually measured. This study actually had a higher overall mortality in the treated group. The Cholestyramine study entered men aged 35–59 with cholesterol levels greater than 265 mg/dl. Only those with triglycerides less than 300 were accepted. Overall mortality was not significantly reduced, due to an increased number of deaths judged to be violent or accidental in the control group. The Gemfibrozil study entered men aged 40–55 with a non-HDL cholesterol greater than 200 mg/dl. Thirty-seven percent had an elevated triglyceride as well as increased cholesterol. A decrease in total mortality was not demonstrated, with more deaths due to violence, accidents, and intracranial hemorrhage in the control group.

In 1988, the National Cholesterol Education Program was released which recommended that serum cholesterol be measured in all adults over 20 years of age. They recommended that those with serum cholesterols below 200 mg/dl have their cholesterol repeated at least every 5 years.

Those with cholesterols between 200 and 239, but without definite coronary heart disease or two other risk factors (male sex itself was one), be given dietary information and have the cholesterol rechecked annually. All others were advised to have their LDL-cholesterol calculated and further decisions be made based on the LDL-cholesterol level.

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